

## Ataxia telangiectasia mutated (ATM) modulates long interspersed element-1 (L1) retrotransposition in human neural stem cells.

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### Public Summary:

Long interspersed element-1 (L1) retrotransposons are sequences of genetic material that are present in the mammalian genome and have the ability of move from one chromosome to another via copy and paste mechanism. L1 mobile elements compose ~20% of the mammalian genome, and ongoing L1 mobility can impact genetic diversity by various mechanisms. Recent data indicate that engineered human L1 is mobile in human embryonic stem cells and in human neural progenitor cells. In this study, we demonstrate an increase in the levels of mobility of an engineered human L1 in cells that lack ataxia telangiectasia mutated gene (ATM), a serine/threonine kinase involved in DNA damage signaling and neurodegenerative disease. We demonstrate that the increase in L1 mobility in ataxia telangiectasia mutated-deficient stem cells most likely occurs by conventional target-site primed reverse transcription and generate either longer, or perhaps more, new L1 events per cell. Finally, we provide evidence suggesting an increase in human-specific L1 DNA copy number in postmortem brain tissue derived from ataxia telangiectasia patients compared with healthy controls. Together, these data suggest that cellular proteins involved in the DNA damage response may modulate L1 mobility and contribute to increased genomic instability in pluripotent stem cells from ATM patients.

### Scientific Abstract:

Long interspersed element-1 (L1) retrotransposons compose approximately 20% of the mammalian genome, and ongoing L1 retrotransposition events can impact genetic diversity by various mechanisms. Previous studies have demonstrated that endogenous L1 retrotransposition can occur in the germ line and during early embryonic development. In addition, recent data indicate that engineered human L1s can undergo somatic retrotransposition in human neural progenitor cells and that an increase in human-specific L1 DNA content can be detected in the brains of normal controls, as well as in Rett syndrome patients. Here, we demonstrate an increase in the retrotransposition efficiency of engineered human L1s in cells that lack or contain severely reduced levels of ataxia telangiectasia mutated, a serine/threonine kinase involved in DNA damage signaling and neurodegenerative disease. We demonstrate that the increase in L1 retrotransposition in ataxia telangiectasia mutated-deficient cells most likely occurs by conventional target-site primed reverse transcription and generate either longer, or perhaps more, L1 retrotransposition events per cell. Finally, we provide evidence suggesting an increase in human-specific L1 DNA copy number in postmortem brain tissue derived from ataxia telangiectasia patients compared with healthy controls. Together, these data suggest that cellular proteins involved in the DNA damage response may modulate L1 retrotransposition.

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